CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73045

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA : #73-045 **SPONSOR: ALPHARMA (A.L. Laboratories)**
DOSAGE FORM: Metered Dose Inhaler (MDI)
STRENGTHS/(s): 90 μg/actuation
TYPE OF STUDY: Pharmacodynamic Bioequivalence Study and a Safety Evaluation Study.
STUDY SITES: [ ]

STUDY SUMMARY: Evaluation of bioequivalence of the test product was based on a pharmacodynamic (methacholine challenge) study performed in 25 mild to moderate asthmatics, and a safety evaluation study in healthy volunteers. These studies were based on the January 27, 1994, OGD interim guidance for albuterol MDI. The assessment of bioequivalence was based on the response scale using methacholine PD20 and Drug Activity Ratio (DAR) as pharmacodynamic metrics. Based on the statistical analyses of these data, 90% confidence intervals comparing the test and reference products were within the [ ]% acceptable limit set forth for albuterol MDI's. The results of this study demonstrate that Alpharma's albuterol MDI, 90 μg/actuation, is bioequivalent to the reference listed drug, Ventolin®, 90 μg/actuation, manufactured by Allen & Hanburys (Glaxo).
The results of the safety evaluation study indicate that the systemic safety profile of Alpharma's albuterol MDI, 90 μg/actuation, is similar to the reference listed drug, Ventolin®, 90 μg/actuation, manufactured by Allen & Hanburys (Glaxo).

IN VITRO PERFORMANCE DATA: *In vitro* performance data submitted by Alpharma on albuterol MDI, 90 μg/actuation, are acceptable. These data indicated that the *in vitro* performance of Alpharma's albuterol MDI, 90 μg/actuation, is comparable to the reference listed drug, Ventolin®, 90 μg/actuation, manufactured by Allen & Hanburys (Glaxo).

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III
INITIAL: /S/ DATE: 7/21/97

GROUP LEADER: Ramakant Mhatre, Ph.D. BRANCH: III
INITIAL: /S/ DATE: 7/22/97

DIRECTOR: Nicholas Fleischer, Ph.D.
DIVISION OF BIOEQUIVALENCE
INITIAL: /S/ DATE: 7/28/97

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: /S/ DATE: 8/8/97

JUL 14 1997

Albuterol Inhalation Aerosol (MDI)
90 µg/actuation
ANDA 73-045
Reviewer: Gur J.P. Singh
73045I.O97

ALPHARMA
(A.L. Laboratories)
Submission Date:
May 23, 1997.

Review of Correspondence Related to In Vitro *Bioequivalence Study Data*

The Division of Bioequivalence *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, issued June 27, 1989, recommends comparative data to characterize *in vitro* performance of the test product relative to that of the reference listed drug (RLD). This guidance (hereafter referred to as the 1989 Guidance) did not set specifications for the requested tests. There is no USP monograph for Albuterol Inhalation Aerosol. However, the data will be compared with the specifications set in USP Chapters 601 and 905, where applicable.

The firm's June 12, 1995, submission provided comparative data. A DBE review of the firm's *in vivo* and *in vitro* data, dated July 17, 1996, included a list of deficiencies of the *in vitro* data, which were communicated to the firm in a July 18, 1996, letter. The firm's August 1,1996, amendment responded to those deficiencies.

Data submitted up to August 1, 1996, were reviewed by the Division of Bioequivalence. Based on the September 3, 1996 review, the Division of Bioequivalence issued a letter to the firm (Letter Date: September 3, 1996) which listed a variety of deficiencies. On September 9 and 11, 1996, the sponsor submitted its responses to these deficiencies. That submission was reviewed and the application was still found to be incomplete. On November 21, 1996, the sponsor was informed of a variety of deficiencies, and it was requested to repeat some of the *in vitro* tests on lots of test and reference products that were still within their expiry dates. The sponsor submitted its response in January 6 and 22, 1997, amendments. These data were reviewed and the application was still found to be incomplete due to a variety of deficiencies. A list of these deficiencies was conveyed to the firm in a tele-conference on February 28,, 1997, and a Division of Bioequivalence letter on May 12, 1997. The sponsor has now submitted another amendment dated May 23, 1997.

This review is based principally on the data submitted on January 6, and 22, and May 23, 1997. Reference is made to previous data, where necessary/applicable.

The MDI's used for *in vitro* testing were from the following batches:

Ventolin^R Inhalation Aerosol 90 µg/actuation (The reference Product), manufactured by Allen & Hanburys, Division of Glaxo, Lot #6ZP0756, Expiry Date: April, 1999

Albuterol Inhalation Aerosol 90 µg/actuation (Test Product), manufactured for A.L. Laboratories by CCL Laboratories Ltd., Runcorn, Chesire, England, Production Lot #8457 Expiry date: December, 1997.

For some tests the sponsor has also submitted data for two additional production batches of the test product (lot #8671- expiry date February 1998, and lot 8834, expiry date April 1998).

Documentation of bioequivalence requires the use of tests based on validated methods. For the tests used for potency estimation and particle size distribution (Andersen cascade [imopactor) the sponsor has used a validated [ ] assay. Albuterol concentrations in various samples were determined by reverse phase [ ] equipped with [ ] detection at [ ] nm. Samples dissolved in methanol were diluted, as required, in the mobile phase (Methanol:Water:Acetic Acid 60:60:0.1, v/v). Required details and data for method validation are given in the January 6, 1997, amendment, a summary of these data are given below:

Accuracy (% of nominal concentrations):

Cascade impaction: % (in the range of µg/mL)

Potency estimation: % (in the range of µg/mL)

Precision (%CV): %

Limit of quantitation: µg/mL with a %CV of

Limit of detection: µg/mL with signal:noise ratio of

Linearity: Linearity was demonstrated for calibration curves based on in the range of µg/mL µg/mL, based on correlation coefficients of or above.

Stability: Data submitted by the sponsor supports stability of samples at room temperature up to 11 days.

The sponsor has used a variety of procedures. Among these procedures, methods used for determination of Unit Spray Sampling and Potency Estimation have been tested by the FDA laboratory in St. Louis. These methods have been found to be satisfactory, based on reviewer's communication with the Division of Chemistry (OGD).

I. Content Uniformity (Unit Spray Content Test)

Estimation of unit dose performed by the firm is equivalent to the potency estimation described in the 1989 Guidance. It is also referred to as unit spray content in USP 23, chapters 601. The flow rate used in this test was 12.5 L/min recommended in the USP as the most satisfactory flow rate (USP, pp 1762). The sponsor has set a specification for unit dose in the range of 75.0% to 125.0% of the label claim . The USP specifications for the uniformity of dosage units are as follows:

> Not more than 1 of the 10 dosage units lies outside the range of 75-125% (μg) of the label claim and no unit lies outside the % (μg) of the label claim.
>
> If the above requirement is not met, test another 20 units. The Content Uniformity is met if no more than 3 (out of 30) units are outside the range of 75-125% of the label claim and no unit lies outside the % of the label claim.

Determination of albuterol per actuation was based on a chemical assay. In this test, a primed unit was actuated into a collection tube attached to a (similar to the USP sampling apparatus/ with a The drug was collected in a mixture of water and methanol and assayed by Based on the January 6 submission (pp 430, vol 13.1), the results are as follows:

Testing Stage	Unit Dose (μg)				Test/Ref (p)
	Test (8457)		Reference		
	Mean	Range	Mean	Range	
Beg. (11-12)	86.1 (10.4)		78.8 (5.4)		1.09 (<0.05)
Mid. (100-101)	75.7 (12.8)		82.5 (3.4)		0.91 (<0.05)
End (199-200)	86.7 (13.3)		87.3 (4.6)		0.99 (>0.05)
Overall	82.8 (13.3)		82.9 (6.1)		0.99 (>0.05)

The *Unit Dose data are given as mean (%CV) of 10 experiments.*

**Out of ten units, three were outside sponsor's specifications of [µg/spray when tested at the middle of the canister life..*

Observations:

- The ranges of unit dose of the test product meet sponsor's specifications at the Beginning and End stages of the MDI life. However *3 of the 10 units at the middle* of the canister life were outside the 75-125% of the label claim, no unit was outside the [ ]% of the label claim.

- On an average the unit dose delivered by the test products was within 10% of that delivered by the reference product. The inter-unit variability for the test product was greater than that of the reference product, as indicated by %CV's given in parentheses.

Because, based on the data submitted by the sponsor on January 6, 1997, the test product did not meet USP test of content uniformity of dosage forms, the sponsor was requested to test content uniformity of additional 30 units of lot #8457, and 10 units of lot #8671 and #8834. These data were submitted on May 23, 1997 (vol 14.1). The results of this testing are summarized as follows:

Testing Stage	Unit Dose (µg)		
	Lot 8457 (n=30)	Lot 8671 (n=10)	Lot 8834 (n=10)
Beg (11-12)	87.2 (13.9), 62.4 - 116.6[a]	82.1 (4.9), 77.0 - 89.4	91.7 (9.0), 72.9-100.4
Mid(100-101)	83.9 (13.6), 69.3-111.9	77.7 (8.2), 63.5- 84.2[c]	91.2 (9.0), 74.0-100.2
End(199-200)	86.1 (15.1), 61.7-116.6[b]	76.5 (5.7), 68.9-82.5	91.5 (8.8), 73.0-100.4

The *Unit Dose data are given as mean (%CV), range.*
[a] two of the 30 units are out of the [ ]% (µg) of the label claim, but all units are within [ ]% (µg) of the label claim.
[b] three of the 30 units are out of the [ ]% (µg) of the label claim, but all units are within [ ]% (µg) of the label claim.
[c] one of the 10 units is out of the [ ]% (µg) of the label claim, but all units are within [ ]% µg) of the label claim.

Observations:

- Based on the results submitted on May 23, 1997, each of the three production lots of the test product meets the USP test of content uniformity at Beginning, Middle and End stages of testing.

- The May 23 amendment contains data for 30 units of lot 8457 in addition to the 10 units tested previously (January 6, 1997 amendment). USP specifications given in USP chapter <905> require a two-step testing, where 10 canisters are tested in the first step and another 20 tested in the second step. If the above data are evaluated in the manner described in the USP, only first 20 of the 30 units' data submitted on May 23 can be considered. If a total of 30 units are considered to be 10 units submitted on January 6 plus 20 units submitted on May 23, then:

  Two of the 30 units are out of the 75-125% of the label claim, but all units are within __% of the label claim, at the Beginning stage.

  Three of the 30 units are out of the 75-125% of the label claim, but all units are within __% of the label claim, at the Middle stage.

  Three of the 30 units are out of the 75-125% of the label claim, but all units are within __% of the label claim, at the End stage.

The test product meets the USP test of content uniformity at the Beginning, Middle and End stages of testing.

II. Shot weight

Measurements of mean shot weights for two actuations at beginning, middle and end of each canister was performed. This test was performed in a manner similar to the test of the metering performance given in the USP (pp 1762), and its procedure was consistent with the 1989 Guidance. The raw data for all testing to determine shot weights are given on pages 430-31 of the January 6, 1997 supplement. Sponsor's specifications for the shot weight are: Overall mean - 77 to 90 mg/spray, and individual determinations to be in the range of mg/spray. The results of shot weight measurements are summarized as follows:

Testing Stage	Shot Weight (mg)				Test/Ref (p)
	Test		Reference		
	Mean	Range	Mean	Range	
Beg. (11-12)	90.0 (2.0)		85.2 (1.9)		1.03 (<0.05)
Mid. (100-101)	86.9 (1.1)		83.8 (2.2)		1.04 (<0.05)
End (199-200)	86.9 (1.5)		84.1 (2.1)		1.03 (<0.05)
Overall	87.8 (2.1)		84.4 (2.1)		1.04 (<0.05)

The shot weight data are given as mean (%CV) of 10 experiments.

Observation:

Based on the shot weight data, test product's performance is comparable to that of the reference product; differences between the test and reference products are less than %. However, it is noteworthy that based on the unit spray content, differences between test and reference products are larger than the difference in shot weights of these products. In reviewer's opinion it may be partly due to differences between the two products in the amount of inactive ingredients delivered per actuation, and partly due to the sensitivity of methods of assessment (i.e., chemical assay versus gravimetric determination).

Shot weight data were also submitted on May 23 for 30 units of lot 8457 and 10 units from each of batches 8671 and 8834 (vol 14.1) All readings are within the above specifications set forth by the sponsor.

III. **Spray Pattern** : The January 6 and May 23, 1997, amendments do not contain new information on spray pattern. Spray pattern testing was performed using the lot #6403 of the test product and lot Z31383LS of the reference products. These batches expired in March 1996. Therefore data submitted on August 1, 1996 is not acceptable for product approval and the review is based on data submitted on June 12, 1995.

The spray pattern was determined on per each of three canisters of test and RLD at each of three distances. Each can was placed in actuator and positioned, 2.5, 5.0 and 7.5 cm away and parallel to a 20 cm X 20 cm spray. spray was fired (the canister was shaken before each spray) for each measurement. The resulting spots were viewed under UV light and the spray pattern was outlined

The reviewer also computed deposition profiles of the three lots of the test product used in this study. The results of these analyses presented in figure 2 (attachment) demonstrate comparable deposition profiles of the three lots of the test product at the beginning of the canister life (actuations 11-25).

IV B. MASS BALANCE: Material balance calculations were performed per USP method. The results of these calculations are summarized below:

Testing Stage	Material Balance (%)	
	Test (lot #8457)	Reference
Beg. (11-25)	99.60 - 118.7	91.31 - 95.23
Mid.(76-90)	103.04 - 108.05	94.71 - 98.49
End (186-200)	107.04 - 127.00	101.16 - 102.95
Beg. (11-25)	103.25 - 117.29 (Test lot #(8671)	
Beg. (11-25)	100.95 - 104.87 (Test lot #(8834)	

Data are tabulated as range for three canisters .

IV C. MMAD and GSD Data

The USP or the 1989 Guidance do not provide specifications for MMAD and GSD.

SPONSOR SPECIFICATIONS:

MMAD: microns
GSD: Specifications not given
Respirable Fraction: Specifications not given

The results of the cascade impactor analysis for MMAD and GSD are given in tables 3 (attachment). The data are based on calculations performed by the reviewer and the sponsor. The reviewer used the computer program written by James Allgire and Moheb Nasr of the FDA St. Louis laboratory. This method uses data for albuterol deposition on stages

Calculation of MMAD and GSD involves the use of Effective Cutoff Diameter (ECD) values. ECD values used by the sponsor were different from those employed by the FDA laboratory (see below).

Impactor Stage	ECD (microns) values used by	
	Sponsor	FDA Lab.
0		
1		
2		
3		
4		
5		
6		
7		
Filter		

Another factor that influences the magnitude of MMAD and GSD values is number of stages included in calculation of these parameters. The sponsor has not mentioned the number of stages used for its analysis. The FDA laboratory's computer program uses data for stages 2-5 for computation of MMAD and GSD. The reviewer has calculated all MMAD and GSD values using that computer program. Separate calculations were done based on ECD values used by the sponsor and the FDA laboratory. The results of these analyses are summarized in table 3 and 4 (attachment).

Observations:

- The sponsor used 15 actuations of the MDI, as recommended in the guidance.

- The MMAD and GSD values (individual as well as mean) calculated by the reviewer are different from those reported by the sponsor, and these differences may be due to the method used for calculations. Furthermore, there was notable difference in the values of MMAD and GSD calculated based on the two ECD's (see table 3 and 4). These differences should not affect the test and reference product comparisons.

- Based on ECD values employed by the firm, MMAD values of the test product were % greater, and its GSD values were similar to the respective values for the reference product. Variation (%CV) was also comparable for these products. In these comparisons, differences in MMAD between the test and reference products were statistically significant (p <0.05).

- Based on ECD values employed by the FDA laboratory, MMAD values of the test product were % greater, and its GSD values were similar to the respective values for the reference product. Variation (%CV) was also comparable for these products. In these comparisons also, differences between the test and reference products were statistically significant (p <0.05).

- Based on the mean or the overall mean values using sponsor's ECD's , the differences between the test and reference products MMAD were μ, and based on reviewer's calculations using FDA Laboratory's ECD's these difference were μ. These differences are also statistically significant. . Nonetheless there is no information available to OGD which indicates that MMAD difference of μ may significantly affect bioavailability of albuterol delivered via an MDI.

- Differences between MMAD values for three production lots of the test product were not statistically significant. These data are indicative of consistency between these lots of the test product.

IV D. Respirable Dose (RD) and Respirable Fraction (RF) Data

$Beta_2$ receptors are located in smooth muscle from large and small airways. Receptors are found in the bronchi, the bronchioles, the airway epithelial cells, and in bronchial submucosal glands from the large bronchi to the terminal bronchioles. They are also found in the alveoli walls, although the pharmacologic significance of this is not known [Carstairs *et al., Am. Rev. Respir. Dis.*, 132: 541(1985)]. The "respirable dose" is frequently taken to be that drug less than microns in diameter (see for example, Vidgren et al., *Pharm. Res.*, 11:1320(1994). Zanen et al., *Intern. J. Pharmac.*, 107: 211(1994), in a study of albuterol delivered as a monodisperse aerosol (NOT from an MDI), found that in mild asthmatics receiving cumulative doses of drug, a micron aerosol (GSD < 1.2) induced a significantly better bronchodilation than did a micron monodisperse aerosol. In view of the above information, to provide further insight into the cascade impactor data, the reviewer computed "respirable doses" and "respirable fractions" based on three different diameters - drug less than microns. Thus, for the micron data, the amount of drug deposited on stages and the filter (i.e., the amount of drug less than microns) was computed. Similarly for the micron data, the amount of drug deposited on stages and the filter, and for the micron data, the amount of drug deposited on stages and the filter. The "respirable fraction" was computed as the "respirable dose" divided by the drug "ex-actuator" (i.e, the sum of drug deposited on the throat, and stages of the cascade impactor and the terminal filter). The results of these calculations are given in tables 5 and 6 (attachment)

Observations:

- For drug less than microns, there were differences between the test and reference products in both the RD and RF, and for most RD's these differences were statistically significant. In the absence of compendial criteria for RD and RF, and the acceptable *in vivo* bioequivalence and safety of the test product, these data are acceptable.

- Differences between RD and RF values for three production lots of the test product were not statistically significant. These data are indicative of consistency between these lots of the test product.

IV E. Microscopy: In response to the agency requests of February 28 and May 23, 1997, the sponsor has performed the USP microscopy particle size test on test product batches 8457, 8671 and 8834 and Ventolin^{R} lot 6ZP0756. The USP test requires estimation of particle of ≥ 10 microns. Data submitted by the firm on microscopical examination of test and reference products are given in volume 14.1. Based on these data particle size distribution of the test product is comparable to that of the reference product.

IV F. Particle Sizing Using The sponsor has also determined the particle size distribution using droplet and particle size analyzer. This test was performed using the lot 6403 of the test product and lot Z31383LS of the reference product, and it was accomplished within the expiry dates of these batches (vol 8.2). The January 6 and May 23, 1997, amendments do not contain new data on this test.

In this experiment each canister was heated for

	Particle size (μM)		Test/Ref	p
	Test	Ref		
Beginning	3.26 (5.23)	2.85 (5.17)	1.14	0.078
Middle	3.18 (3.31)	3.03 (4.58)	1.05	0.033
End	3.26 (0.71)	2.92 (6.53)	1.12	0.054
Overall	3.23 (3.34)	2.93 (5.45)	1.10	0.002

Observations:

- Immediately before testing MDI canisters were
  This is inconsistent with the recommended clinical use of albuterol MDI's. Any procedure used

  Therefore, the reviewer is not certain if these data has any relevance to the clinical use of albuterol MDI. However, during the November 21, 1996 tele-conference with the firm, OGD did not recommend a repetition of this test at the ambient temperature. Therefore the review is based on the data submitted previously.

- On an average the size of particles emitted by the test product was 10% greater than that of the reference product , and the difference between these products was statistically significant. However, in the absence of compendial criteria, and the acceptable *in vivo* bioequivalence and saftety of the test product, these data are acceptable.

V. Deposition of Emitted dose by Twin Impinger:

The apparatus used for this test was identical to the USP "Single Stage Impactor Apparatus 2" (USP, pp 1765). This apparatus is used to determine the fine particle size fraction of the dose discharged from MDI's through the inhalation actuator. When operated at an airflow rate of 60L/min, the lower impinger provides an aerodynamic particle cut off size of μM. Particles μM are trapped in the upper chamber, and particles μM are collected in the lower chamber.

The sponsor performed the test according to the USP. This test was performed using the lot #6403 of the test product and lot Z31383LS of the reference product, and it was accomplished within the expiry dates of these batches (vol 8.2 and 10.1). In this test primed MDI's were actuated into the impinger operated at an airflow rate of 60 ± 5 L/min. For each test 10 actuations (2 + 8, as recommended in the USP) were used. At the end of 10 actuations the apparatus was rinsed with methanol. Stage 1 washings included those from the mouthpiece to the round bottom flask. Stage 2 washings included those from the inner and outer areas of stage 2, inlet tube assembly and the conical flask. The washings were transferred to 50 mL volumetric flasks and diluted with methanol. The amount of albuterol in these samples was determined using an assay. Procedures used for calculation of μg albuterol/actuation, % retained in stage 1 and stage 2 are given on pp 82 (volume 10.1).

The results of twin impinger analysis performed by the firm are given below. These data are based on previous submissions, no new data were submitted on January 6 and May 23, 1997.

	Albuterol Deposition (μg) Per Actuation			
	Test	Ref	Test/Ref	p
Upper Impingement Chamber	41.09 (5.31)	33.21 (9.79)	1.24	0.008
Lower Impingement Chamber	44.14 (3.90)	56.84 (4.82)	0.78	0.001
Respirable Fraction	0.54 (2.99)	0.57 (4.79)	0.95	0.064

Observation:

Deposition of albuterol at the upper and lower chambers was different between the test and the reference product, and these differences were statistically significant. It is noteworthy that unlike the reference product, the test product spray deposited approximately same amount of albuterol in the upper and lower chambers. However, in the absence of compendial criteria, and the acceptable *in vivo* bioequivalence and safety of the test product, these data are acceptable.

VII. Overall Comment

The sponsor has submitted *in vitro* performance data on several batches of the test product. As mentioned in the beginning of this review the Agency had requested the

sponsor at several occasions to perform additional *in vitro* testing . Some of the tests were requested at a stage when the batches used for the *in vivo* bioequivalence study (test: lot#6403 and the reference lot#Z31383LS) had already expired. The data submitted by the sponsor on expired batches were considered to be unacceptable.

Evaluation of some tests of the *in vitro* performance is based on three production lots of the test product and a new lot of the reference product, because requests for repetition of these tests by the Agency were made after expiration of test and reference products used for the bioequivalence study. Thus, data for uniformity of unit dose and two tests of particle size determination (Andersen cascade impactor and Microscopy) are based on new lots. These data are indicative of comparable *in vitro* performance of the test and the reference product, and consistency among the three product lots of the test product.

VIII. Recommendations

1. The *in vitro* performance testing conducted by ALPHARMA (A.L. Laboratories) comparing its albuterol 90 μg per actuation Metered Dose Inhaler Lot# 8457 with the reference product, Ventolin^R 90 μg per actuation Metered Dose inhaler (lot #6ZP076) has been found to be acceptable to the Division of Bioequivalence. Furthermore, *in vitro* performance data submitted by ALPHARMA comparing three lots (#8457, #8671 and #8834) of its albuterol 90 μg per actuation Metered Dose Inhaler are acceptable to the Division of Bioequivalence.

   The *in vitro* testing should be incorporated into firm's manufacturing and stability programs. The test product should conform to USP test of content uniformity (USP chapter <905>). The Division of Bioequivalence recommends the following specifications as tentative based on data submitted by the firm:

   MMAD: microns
   GSD

   Respirable fraction: Not less than
   Respirable dose: Not less than μg)

   Respirable fraction and respirable are based on drug microns.

2. An *in vivo* bioequivalence study and a safety evaluation study conducted by this firm on the test product have been found to be acceptable to the Division of Bioequivalence (see DBE review dated April 29, 1997). The sponsor has

therefore met requirements of in vivo bioequivalence and in vitro performance testing on its albuterol metered dose inhaler, 90 μg/actuation.

/S/

Gur Jai Pal Singh, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR /S/ 12/5/1997

CONCUR: /S/ DATE 7/14/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

GJP SINGH/ 6-18-97. 73-045I.O97

CC: ANDA# 73-045 (Original, duplicate), HFD-600 (Hare), HFD-130 (Jallen), HFD-655 (Nerurkar, Singh), Drug file, Division file.

ATTACHMENTS

Table 1A: Deposition of albuterol at various stages of the Andersen cascade imactor. (AL-LAB's 8457)

Total Deposition (15 Actuations)

	Beginning			Middle			End			Mean				%CV			
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Total	Beg	Mid	End	Total	Beg	Mid	End
0	12.36	24.41	13.31	14.51	13.79	9.43	11.72	17.3	11.78	14.3	16.69	12.58	13.60	30.6	40.1	21.9	23.6
1	15.34	18.02	14.67	13.83	14.92	13.31	15.23	19.18	13.45	15.3	16.01	14.02	15.95	13.2	11.1	5.9	18.4
2	28.61	35.31	36.99	26.96	32.79	26.05	32.63	44.15	32.08	32.8	33.64	28.60	36.29	17.0	13.2	12.8	18.8
3	127.72	141.19	148	121.47	130.26	118.21	101.99	175.92	143.89	134	138.97	123.31	140.60	15.8	7.43	5.1	26.4
4	233.59	221.37	236.67	232.55	222.36	208.58	250.42	263.74	223.62	233	230.54	221.16	245.93	7.1	3.51	5.4	8.3
5	116.53	121.32	125.92	121.21	109.29	114.46	123.36	121.67	113.76	119	121.26	114.99	119.60	4.5	3.87	5.2	4.3
6	16.4	17.01	14.79	15.64	16.39	15.84	17.13	14.46	13.36	15.7	16.07	15.96	14.98	8.0	7.14	2.4	12.9
7	6.53	7.8	8.39	8.12	8.77	7.63	6.72	7.42	7.5	7.65	7.57	8.17	7.21	9.5	12.6	7.0	5.9
Filter	5.62	8.54	6.07	12.44	9.38	8.02	17.98	19.41	6.45	10.4	6.74	9.95	14.61	49.1	23.3	22.8	48.6
Valve Stem	42.12	43.54	70.53	42.48	43.73	96.14	41.43	41.24	96.71	57.5	52.06	60.78	59.79	41.5	30.7	50.4	53.5
Actuator	194.9	184.16	115.47	146.65	164.99	169.53	160.74	166.8	177.32	165	164.84	160.39	168.29	14.0	26.1	7.6	5.0
Ind. Port	1049.39	820.17	784.31	907.55	913.92	803.27	1069.23	1074.88	808.29	915	884.62	874.91	984.13	13.2	16.3	7.1	15.5
Total	1849.12	1642.85	1575.14	1663.4	1680.6	1590.47	1848.58	1966.18	1648.21	1718	1689.04	1644.82	1820.99	7.9	8.45	2.9	8.8

Deposition/ Actuation

	Beginning			Middle			End			Mean				%CV			
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Total	Beg	Mid	End	Total	Beg	Mid	End
0	0.82	1.63	0.89	0.97	0.92	0.63	0.78	1.15	0.79	0.95	1.11	0.84	0.91	30.6	40.1	21.9	23.6
1	1.02	1.20	0.98	0.92	0.99	0.89	1.02	1.28	0.90	1.02	1.07	0.93	1.06	13.2	11.1	5.9	18.4
2	1.91	2.35	2.47	1.80	2.19	1.74	2.18	2.94	2.14	2.19	2.24	1.91	2.42	17.0	13.2	12.8	18.8
3	8.51	9.41	9.87	8.10	8.68	7.88	6.80	11.73	9.59	8.95	9.26	8.22	9.37	15.8	7.43	5.1	26.4
4	15.57	14.76	15.78	15.50	14.82	13.91	16.69	17.58	14.91	15.5	15.37	14.74	16.40	7.1	3.51	5.4	8.3
5	7.77	8.09	8.39	8.08	7.29	7.63	8.22	8.11	7.58	7.91	8.08	7.67	7.97	4.5	3.87	5.2	4.3
6	1.09	1.13	0.99	1.04	1.09	1.06	1.14	0.96	0.89	1.04	1.07	1.06	1.00	8.0	7.14	2.4	12.9
7	0.44	0.52	0.56	0.54	0.58	0.51	0.45	0.49	0.50	0.51	0.50	0.54	0.48	9.5	12.6	7.0	5.9
Filter	0.37	0.57	0.40	0.83	0.63	0.53	1.20	1.29	0.43	0.7	0.45	0.66	0.97	49.1	23.3	22.8	48.6
Valve Stem	2.81	2.90	4.70	2.83	2.92	6.41	2.76	2.75	6.45	3.84	3.47	4.05	3.99	41.5	30.7	50.4	53.5
Actuator	12.99	12.28	7.70	9.78	11.00	11.30	10.72	11.12	11.82	11	10.99	10.69	11.22	14.0	26.1	7.6	5.0
Ind.Port	69.96	54.68	52.29	60.50	60.93	53.55	71.28	71.66	53.89	61	58.97	58.33	65.61	13.2	16.3	7.1	15.5
Total	123.27	109.52	105.01	110.89	112.04	106.03	123.24	131.08	109.88	115	112.60	109.65	121.40	7.9	8.45	2.9	8.8

Table 1B: Deposition of albuterol at various stages of the Andersen cascade imactor. (Ventolin, 6ZP0756)

Total Deposition (15 Actuations)

	Beginning			Middle			End			Mean				%CV			
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Total	Beg	Mid	End	Total	Beg	Mid	End
0	7.67	9.74	9.33	8.05	10.15	13.33	11.14	9.56	12.49	10.2	8.91	10.51	11.06	18.5	12.3	25.3	13.3
1	10.72	12.51	12.87	9.8	11.18	13.39	15.07	11.04	14.2	12.3	12.03	11.46	13.44	14.2	9.57	15.8	15.8
2	19.22	26.5	21.09	19.93	27.96	24.63	23.32	24.43	24.64	23.5	22.27	24.17	24.13	12.5	17	16.7	2.9
3	94.53	96.68	104.19	96.2	97.24	109.25	102.06	96.91	108.89	101	98.47	100.90	102.62	5.6	5.15	7.2	5.9
4	217.93	235.85	251.53	234.15	238.34	257.57	250.5	251.34	256.3	244	235.10	243.35	252.71	5.4	7.15	5.1	1.2
5	200.8	189.77	198.54	222.07	211.85	205.59	223.62	232.39	222.82	212	196.37	213.17	226.28	6.7	2.97	3.9	2.3
6	20.41	20.31	20.29	22.3	21.06	20.32	22.59	23.09	22.05	21.4	20.34	21.23	22.58	5.3	0.32	4.7	2.3
7	6.2	6.28	6.89	6.88	7.46	7.05	6.27	6.96	6.42	6.71	6.46	7.13	6.55	6.5	5.85	4.2	5.5
Filter	6.15	17.73	22.59	20.73	10.51	21.87	17.63	24.25	19.86	17.9	15.49	17.70	20.58	33.2	54.5	35.3	16.4
Valve Stem	9.15	14.68	13.93	13.03	11.55	12.79	9.4	14.47	12.38	12.4	12.59	12.46	12.08	16.3	23.8	6.4	21.1
Actuator	156.61	134.6	135.6	139.98	123.34	127.22	137.71	150.97	143.55	139	142.27	130.18	144.08	7.6	8.74	6.7	4.6
Ind. Port	725.38	739.08	801.97	716.34	758.9	767.26	699.36	716.34	796.06	747	755.48	747.50	737.25	4.9	5.41	3.7	7.0
Total	1474.77	1524.86	1629.29	1514.8	1555.85	1597.58	1461.73	1530.78	1627.03	1546	1542.97	1556.08	1539.85	4.0	5.11	2.7	5.4

Deposition/ Actuation

	Beginning			Middle			End			Mean				%CV			
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Total	Beg	Mid	End	Total	Beg	Mid	End
0	0.51	0.65	0.62	0.54	0.68	0.89	0.74	0.64	0.83	0.68	0.59	0.70	0.74	18.5	12.3	25.3	13.3
1	0.71	0.83	0.86	0.65	0.75	0.89	1.00	0.74	0.95	0.82	0.80	0.76	0.90	14.2	9.57	15.8	15.8
2	1.28	1.77	1.41	1.33	1.86	1.64	1.55	1.63	1.64	1.57	1.48	1.61	1.61	12.5	17	16.7	2.9
3	6.30	6.45	6.95	6.41	6.48	7.28	6.80	6.46	7.26	6.71	6.56	6.73	6.84	5.6	5.15	7.2	5.9
4	14.53	15.72	16.77	15.61	15.89	17.17	16.70	16.76	17.09	16.2	15.67	16.22	16.85	5.4	7.15	5.1	1.2
5	13.39	12.65	13.24	14.80	14.12	13.71	14.91	15.49	14.85	14.1	13.09	14.21	15.09	6.7	2.97	3.9	2.3
6	1.36	1.35	1.35	1.49	1.40	1.35	1.51	1.54	1.47	1.43	1.36	1.42	1.51	5.3	0.32	4.7	2.3
7	0.41	0.42	0.46	0.46	0.50	0.47	0.42	0.46	0.43	0.45	0.43	0.48	0.44	6.5	5.85	4.2	5.5
Filter	0.41	1.18	1.51	1.38	0.70	1.46	1.18	1.62	1.32	1.19	1.03	1.18	1.37	33.2	54.5	35.3	16.4
Valve Stem	0.61	0.98	0.93	0.87	0.77	0.85	0.63	0.96	0.83	0.83	0.84	0.83	0.81	16.3	23.8	6.4	21.1
Actuator	10.44	8.97	9.04	9.33	8.22	8.48	9.18	10.06	9.57	9.26	9.48	8.68	9.61	7.6	8.74	6.7	4.6
Ind.Port	48.36	49.27	53.46	47.76	50.59	51.15	46.62	47.76	53.07	49.8	50.37	49.83	49.15	4.9	5.41	3.7	7.0
Total	98.32	101.66	108.62	100.99	103.72	106.51	97.45	102.05	108.47	103	102.86	103.74	102.66	4.0	5.11	2.7	5.4

Table 2: Deposition of albuterol at various stages of the Andersen cascade imactor (Test Product Lots)

Total Deposition (15 Actuations)

	lot # 8457			Lot #8671			Lot #8834			Mean			%CV		
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	8457	8671	8834	8457	8671	8834
0	12.36	24.41	13.31	16.96	13.44	9.5	10.35	9.72	12.74	16.69	13.30	10.94	40.1	28.1	14.6
1	15.34	18.02	14.67	17.13	14.52	12.03	11.02	9.33	11.02	16.01	14.56	10.46	11.1	17.5	9.3
2	28.61	35.31	36.99	39.52	29.97	27.67	21.23	21.81	20.75	33.64	32.39	21.26	13.2	19.4	2.5
3	127.72	141.19	148	130.26	120.61	110.76	102.81	110.92	102.41	138.97	120.54	105.38	7.43	8.1	4.6
4	233.59	221.37	236.67	210.66	195.65	194.75	220.42	222.97	215.88	230.54	200.35	219.76	3.51	4.5	1.6
5	116.53	121.32	125.92	154.89	146.07	151.25	163.75	145.38	157.02	121.26	150.74	155.38	3.87	2.9	6.0
6	16.4	17.01	14.79	23.12	21.88	23.83	19.35	18.48	20.34	16.07	22.94	19.39	7.14	4.3	4.8
7	6.53	7.8	8.39	9.25	9.33	9.59	12.1	7.62	7.87	7.57	9.39	9.20	12.6	1.9	27.4
Filter	5.62	8.54	6.07	20.71	6.14	2.98	8.41	9.18	10.11	6.74	9.94	9.23	23.3	95.1	9.2
Valve Stem	42.12	43.54	70.53	50.44	56.79	41.95	40.25	35.95	54.14	52.06	49.73	43.45	30.7	15.0	21.9
Actuator	194.9	184.16	115.47	206.84	151.43	159.87	174.45	150.66	231.59	164.84	172.71	185.57	26.1	17.3	22.4
Ind. Port	1049.39	820.17	784.31	973.58	849.46	972.54	835.97	803.03	850.08	884.62	931.86	829.69	16.3	7.7	2.9
Total	1849.12	1642.85	1575.14	1853.4	1615.29	1716.72	1620.09	1545.05	1693.96	1689.04	1728.46	1619.70	8.45	6.9	4.6

Deposition/ Actuation

	lot # 8457			Lot #8671			Lot #8834			Mean			%CV		
Stage	Can1	Can 2	Can 3	Can1	Can 2	Can 3	Can1	Can 2	Can 3	8457	8671	8834	8457	8671	8834
0	0.82	1.63	0.89	1.13	0.90	0.63	0.69	0.65	0.85	1.11	0.89	0.73	40.1	28.1	14.6
1	1.02	1.20	0.98	1.14	0.97	0.80	0.73	0.62	0.73	1.07	0.97	0.70	11.1	17.5	9.3
2	1.91	2.35	2.47	2.63	2.00	1.84	1.42	1.45	1.38	2.24	2.16	1.42	13.2	19.4	2.5
3	8.51	9.41	9.87	8.68	8.04	7.38	6.85	7.39	6.83	9.26	8.04	7.03	7.43	8.1	4.6
4	15.57	14.76	15.78	14.04	13.04	12.98	14.69	14.86	14.39	15.37	13.36	14.65	3.51	4.5	1.6
5	7.77	8.09	8.39	10.33	9.74	10.08	10.92	9.69	10.47	8.08	10.05	10.36	3.87	2.9	6.0
6	1.09	1.13	0.99	1.54	1.46	1.59	1.29	1.23	1.36	1.07	1.53	1.29	7.14	4.3	4.8
7	0.44	0.52	0.56	0.62	0.62	0.64	0.81	0.51	0.52	0.50	0.63	0.61	12.6	1.9	27.4
Filter	0.37	0.57	0.40	1.38	0.41	0.20	0.56	0.61	0.67	0.45	0.66	0.62	23.3	95.1	9.2
Valve Stem	2.81	2.90	4.70	3.36	3.79	2.80	2.68	2.40	3.61	3.47	3.32	2.90	30.7	15.0	21.9
Actuator	12.99	12.28	7.70	13.79	10.10	10.66	11.63	10.04	15.44	10.99	11.51	12.37	26.1	17.3	22.4
Ind.Port	69.96	54.68	52.29	64.91	56.63	64.84	55.73	53.54	56.67	58.97	62.12	55.31	16.3	7.7	2.9
Total	123.27	109.52	105.01	123.56	107.69	114.45	108.01	103.00	112.93	112.60	115.23	107.98	8.45	6.9	4.6

Table 3: MMAD and GSD values calculated from data submitted on January, 6, 1997 using the ECD values given by the firm and those used by the FDA's St. Louise laboratory.

A: Based on Firms' ECD values

MMAD

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	3.94	1.4	3.51	0.5	1.12	<0.05
Mid (76-90)	3.82	1.3	3.48	2.9	1.10	<0.05
End (186-200)	3.87	3.2	3.46	0.9	1.12	<0.05
Overall	3.88	2.3	3.48	1.7	1.11	<0.05

GSD

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	1.56	1.9	1.54	1.3	1.01	>0.05
Mid (76-90)	1.56	0.4	1.55	1.1	1.00	>0.05
End (186-200)	1.55	1.3	1.56	0.6	1.00	>0.05
Overall	1.56	1.2	1.55	1.0	1.00	>0.05

B: Based on the ECD values used by the FDA lab.

MMAD

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	2.52	2.0	2.19	0.7	1.15	<0.05
Mid (76-90)	2.57	1.5	2.31	3.4	1.11	<0.05
End (186-200)	2.60	3.7	2.30	1.1	1.13	<0.05
Overall	2.56	2.6	2.26	3.2	1.13	<0.05

GSD

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	1.74	2.7	1.72	1.5	1.01	>0.05
Mid (76-90)	1.65	0.6	1.64	1.1	1.01	>0.05
End (186-200)	1.64	1.9	1.65	0.7	0.99	>0.05
Overall	1.68	3.2	1.67	2.4	1.00	>0.05

Table 4: MMAD and GSD values for three lots of the test product calculated from data submitted on January, 6, 1997 using the ECD values given by the firm and those used by the FDA's St. Louise laboratory.

A: Based on Firms' ECD values

	MMAD			GSD		
	Lot #			Lot#		
	8457	8671	8834	8457	8671	8834
Can 1	3.89	3.71	3.57	1.54	1.63	1.55
Can 2	4.00	3.74	3.63	1.59	1.58	1.53
Can 3	3.92	3.65	3.61	1.54	1.56	1.56
Mean	3.94	3.70	3.60	1.56	1.59	1.55
%CV	1.4	1.2	0.8	1.9	2.3	1.0
8457/8671	1.06			0.98		
8457/8838	1.09			1.01		

B: Based on ECD values used by the FDA lab.

	MMAD			GSD		
	Lot #			Lot#		
	8457	8671	8834	8457	8671	8834
Can 1	2.48	2.35	2.23	1.71	1.63	1.73
Can 2	2.58	2.51	2.42	1.79	1.58	1.62
Can 3	2.51	2.44	2.40	1.72	1.56	1.65
Mean	2.52	2.43	2.35	1.74	1.59	1.67
%CV	2.0	3.3	4.4	2.5	2.3	3.4
8457/8671	1.04			1.09		
8457/8838	1.07			1.04		

Table 5: Respirable Dose and Respirable Fraction data based on January 6, 1997 amendment. ANDA #73-045

Drug < 5.8 microns

Respirable Dose

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	36.99	3.8	39.63	5.0	0.93	< 0.05
Middle (76-90)	34.81	4.0	41.84	2.6	0.83	< 0.05
End (186-200)	38.61	10.1	43.70	1.3	0.88	< 0.05
Overall	36.80	7.5	41.72	5.1	0.88	< 0.05

Respirable Fraction

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	0.38	11.3	0.43	0.9	0.88	> 0.05
Middle (76-90)	0.37	2.4	0.45	2.0	0.82	< 0.05
End (186-200)	0.37	8.1	0.46	3.3	0.80	< 0.05
Overall	0.37	7.4	0.45	3.5	0.82	< 0.05

Drug < 4.7 microns

Respirable Dose

	TEST (8457)		REF		TEST/REF	p
	Mean	%CV	Mean	%CV		
Beg (11-25)	34.74	3.3	38.15	5.1	0.91	> 0.05
Middle (76-90)	32.90	4.0	40.23	2.9	0.82	< 0.05
End (186-200)	36.20	9.6	42.09	1.2	0.86	< 0.05
Overall	34.61	6.9	40.16	5.2	0.86	< 0.05

Respirable Fraction

	TEST (8457)		REF		TEST/REF	p
	Mean	%CV	Mean	%CV		
Beg (11-25)	0.36	10.7	0.42	0.2	0.86	< 0.05
Middle (76-90)	0.35	2.8	0.43	2.7	0.81	< 0.05
End (186-200)	0.34	8.1	0.45	3.3	0.76	< 0.05
Overall	0.35	7.1	0.43	3.6	0.81	< 0.05

Drug <3.3 microns

Respirable Dose

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	25.48	2.2	31.58	5.2	0.81	< 0.05
Middle (76-90)	24.68	4.9	33.51	2.4	0.74	< 0.05
End (186-200)	26.82	8.2	35.25	1.7	0.76	< 0.05
Overall	25.66	6.2	33.45	5.5	0.77	< 0.05

Respirable Fraction

	TEST (8457)		REF		TEST/REF	*p*
	Mean	%CV	Mean	%CV		
Beg (11-25)	0.26	9.2	0.35	0.3	0.74	< 0.05
Middle (76-90)	0.26	3.9	0.36	3.3	0.72	< 0.05
End (186-200)	0.25	4.5	0.37	4.2	0.68	< 0.05
Overall	0.26	5.7	0.36	4.3	0.72	< 0.05

Table 6: Respirable Dose and Respirable Fraction data based on January 6, 1997 amendment. ANDA #73-045. Comparison of the three lots of the test product at the Begining testing stage

Respirable Dose

	LOT #									
	8457 (X)		8671 (Y)		8834 (Z)		X/Y	(p)	X/Z	(p)
	Mean	%CV	Mean	%CV	Mean	%CV				
Drug <5.8 microns	36.99	3.8	36.42	6.7	35.97	1.4	1.02	(>0.05)	1.03	(>0.05)
Drug <4.7 microns	34.74	3.3	34.26	5.9	34.56	1.4	1.01	(>0.05)	1.01	(>0.05)
Drug <3.3 microns	25.88	2.2	26.22	5.6	27.53	2.5	0.99	(>0.05)	0.94	(<0.05)

Respirable Fraction

	LOT #									
	8457 (X)		8671 (Y)		8834 (Z)		X/Y	(p)	X/Z	(p)
	Mean	%CV	Mean	%CV	Mean	%CV				
Drug <5.8 microns	0.38	11.3	0.36	4.7	0.39	2.0	1.06	(>0.05)	0.97	(>0.05)
Drug <4.7 microns	0.36	10.7	0.34	4.4	0.37	1.9	1.06	(>0.05)	0.97	(>0.05)
Drug <3.3 microns	0.26	9.2	0.26	3.3	0.30	1.6	1.00	(>0.05)	0.87	(>0.05)

Figure 1: Albuterol deposition profiles based on the cascade impactor data submitted on January 6, 1997 (ANDA #73-045)

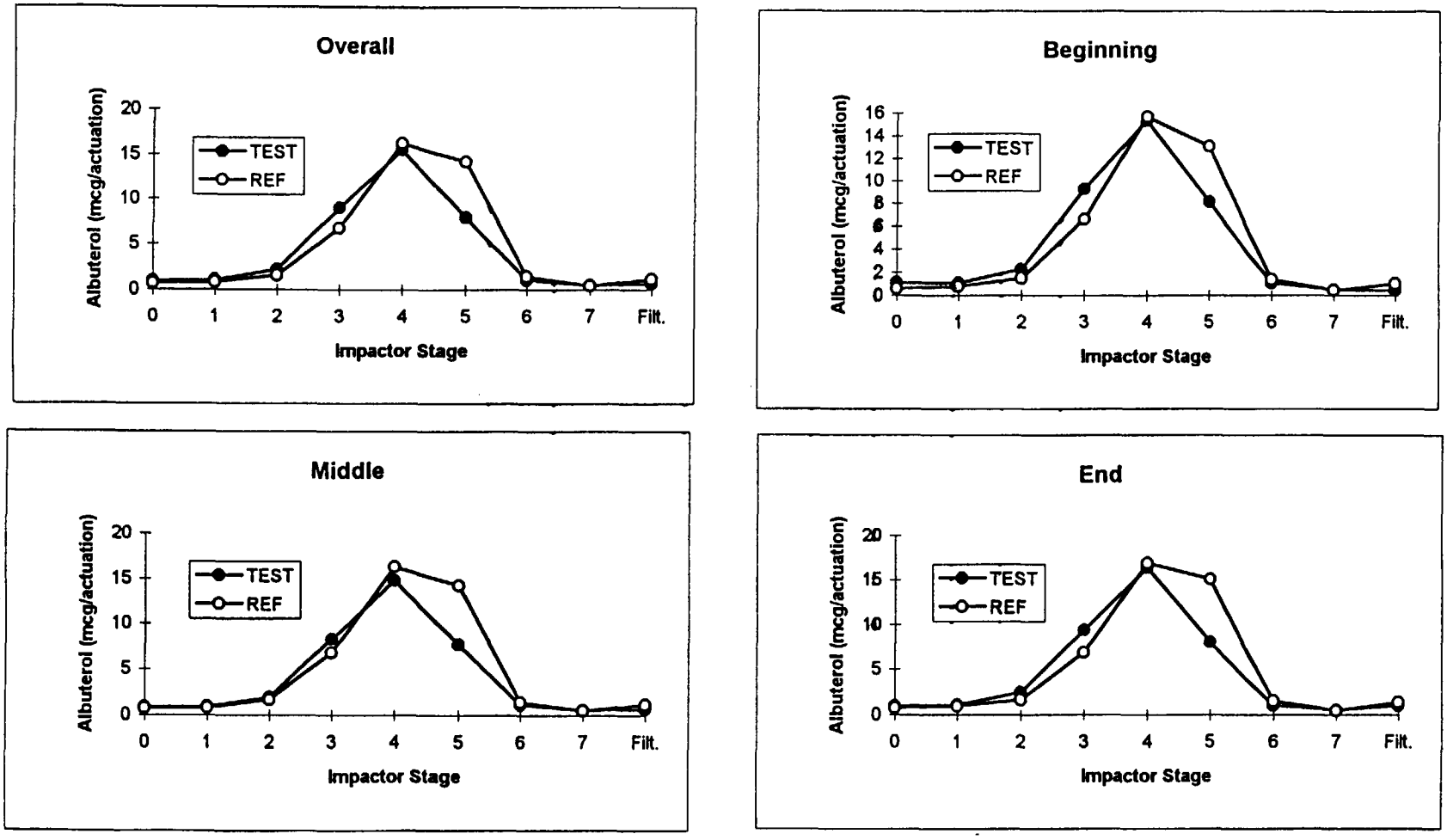
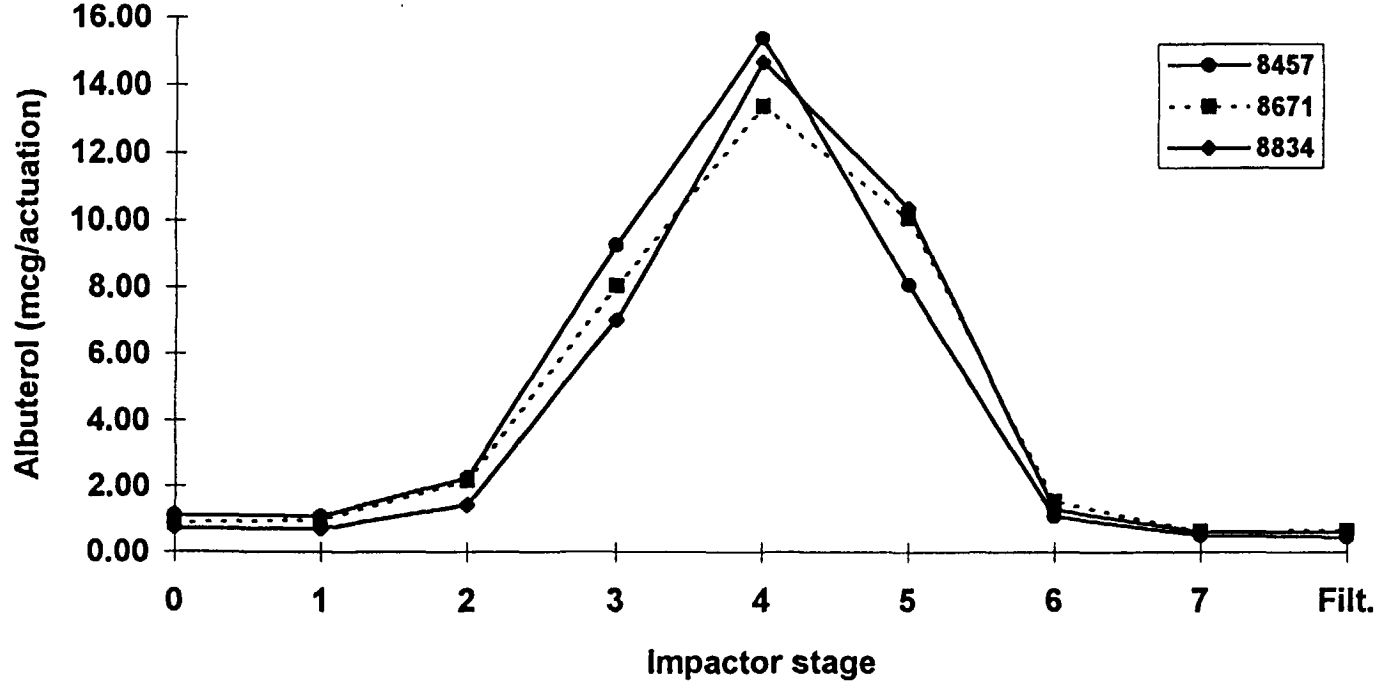


Figure 2: Albuterol deposition profiles for three lots of the test product based on data submitted on January 6, 1997 (ANDA #73-045)



APR 29 1997

Albuterol Inhalation Aerosol (MDI)
90 µg/actuation
ANDA 73-045
Reviewer: Gur J.P. Singh
73045def.197

A.L. Laboratories
Submission Date:
~~Sept 20~~ and Nov. 15, 1996,
Oct 8) Jan. 6 and 22, 1997

Review of Correspondence Related to In Vitro *Bioequivalence Study Data*

The Division of Bioequivalence (DBE) *Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers)*, issued June 27, 1989, recommends comparative data to characterize *in vitro* performance of the test product relative to that of the reference listed drug.

The firm's June 12, 1995, submission provided comparative data for the test and the reference product. A DBE review of the firm's *in vivo* and *in vitro* data, dated July 17, 1996, included a list of deficiencies which were communicated to the firm in a July 18, 1996 letter. The firm's August 1,1996, amendment responded to those deficiencies.

Data submitted up to August 1, 1996 were reviewed by the Division of Bioequivalence. Based on the September 3, 1996 review, the Division of Bioequivalence issued a letter to the firm (Letter Date: September 3, 1996). With regard to the *in vitro* performance data this letter listed a variety of deficiencies. On September 20 and November 15, 1996, the sponsor submitted its responses to these deficiencies. These submissions were reviewed and the application was still found to be incomplete. On November 21, 1996, the sponsor was informed of a variety of deficiencies, and it was requested to repeat some of the *in vitro* tests on lots of test and reference products within their expiry date. The sponsor submitted response to these deficiencies on January 6 and 22, 1997.

Data submitted up to January 22, 1997 were reviewed, and application was still found to be incomplete due to the deficiencies given below. The sponsor was informed of these deficiencies in a tele-conference on February 28, 1997, and via fax on March 5, 1997 (attachments).

Deficiencies:

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Recommendation

1. The in vitro performance data submitted by A.L. Laboratories on its albuterol metered dose inhaler has been found to be incomplete due to deficiencies #1 and 2. The sponsor was informed of these deficiencies previously. Further review of this application will not be conducted till the sponsor submits satisfactory response to deficiencies #1 and 2 .

/S/

Gur Jai Pal Singh, Ph.D.
Division of Bioequivalence
Review Branch II

/S/

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR _____ 4/29/1997

CONCUR: /S/ DATE 4/29/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

GJP SINGH/ 4/29/97 73045def.197

CC: ANDA# 73-045 (Original, duplicate), HFD-600 (Hare), HFD-130 (Jallen), HFD-655 (Nerurkar, Singh), Drug file, Division file.

APR 29 1997

Albuterol Inhalation Aerosol
90 µg/actuation
ANDA **73-045**
Reviewer: Z.Z. Wahba
73045s3.695

A.L. Laboratories
Baltimore, MD
Submission Dates:
September 09, 1996
September 11, 1996

AMENDMENT TO A REVIEWED IN VIVO BIOEQUIVALENCE STUDY
(Continuation of the Review Dated Sept. 03, 1996)

BACKGROUND

The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated 9/03/96, ANDA #73-045) due to problems cited in the deficiency comments.

In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

Comment #1
The following items are needed for completion of the evaluation of the in vivo bioequivalence study. These items should be provided on paper copies (spread sheets) as well as on a floppy diskette (ASCII formate):

> Complete raw data for all FEV_1 measurements, during screening and subject inclusion phases for the 25 subjects used in the bioeqivalence study. This should include baseline FEV_1 measurements for each study day including subject screening and inclusion phase, as well as all FEV_1 measurements associated with each and every challenge dose. The number of breaths of methacholine associated with each and every challenge dose should also be reported.

Response to Comment #1

> The firm has provided the raw data that was requested in comment #1.
>
> The firm's response to comment #1 is acceptable.

Comment #1a

> Raw data on subject inclusion qualification criteria showing that there was a minimum eight-fold increase over baseline in response to two actuations of Ventolin® Inhalation Aerosol and a minimum two-fold ratio of response to two actuations relative to one actuation of Ventolin® Inhalation Aerosol. Include an example(s) of the method of calculation

that was used for subject inclusion qualification criteria.

Response to Comment #1a

The firm has provided the raw data that was requested in comment #1a. In addition to examples of the method of calculation.

The firm's response to comment #1a is acceptable.

Comment #1b

With regard to the data on the individual FEV_1 efforts for the bronchoprovocation study (Data submitted by the firm on June 19, 1995, in two tables, located in volume B9.1, p #05-#25).

i. For Table #1 (baseline FEV_1 data prior to morning and afternoon challenges for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

ii. For Table #2 (raw FEV_1 data for treatment phases only).

The data for subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 are not provided.

Response to Comment #1b

Subjects #113, 114, 115, 116, 119, 121, 122 (visits 1, 2 and 3) and 123 were tested on a Koko spirometer from which there is no paper tape printout, and only the highest FEV_1 of each set was recorded. The firm has provided the data that was requested in two Tables (see volume #B11.1, pages 9-10 and 37-64).

The firm's response to comment #1b is acceptable.

Comment #2

Please provide the equation that was used to estimate the Post-albuterol PD_{20} (cumulative mg). In addition, the firm should provide examples of its calculations for this value for a number of subjects. These examples should include subjects who had relatively high and relatively low post-albuterol PD_{20} values.

Response to Comment #2

The equation is

$$PD_{20} = \text{Dose 1} + \frac{(\text{Dose 2} - \text{Dose 1})(20 - \text{Response 1})}{(\text{Response 2} - \text{Response 1})}$$

Where:

Dose 1= second to last dose resulted in just less than a % decrease in FEV_1 compared to Saline FEV_1
Dose 2= last dose resulted in a % decrease in FEV_1 compared to Saline FEV_1
Response 1= % decrease in FEV_1 caused by Dose 1
Response 2= % decrease in FEV_1 caused by Dose 2

- The firm provided number of examples for its calculation (see, vol. #B11.1, pages 10-13 and 37-58).

The firm's response to comment #2 is acceptable.

Comment #3

In the validation report section (Vol. A8.1, page #116), the firm is requested to provide equations and its calculations for subject #1, both morning and afternoon visits.

Response to Comment #3

The requested information is provided in volume #B11.1, on pages 14, 59 and 60.

The firm's response to comment #3 is acceptable.

Comment #4

The raw data for the challenge studies should include the actual date of dosing of the treatment phase, gender and age, body weight, height, and predicted FEV_1 for age, gender and height, in addition to the data on baseline , saline control and FEV_1 at each challenge dose.

Response to Comment #4

The requested information is provided in volume #B11.1, on pages 61-64.

The firm's response to comment #4 is acceptable.

Statistical Analysis and Comparative In Vivo Performance:

The statistical analysis to determine bioequivalence of the test and reference products was based on the `response scale'. Analyses of the data were performed by the Division of Biometrics, HFD-700.

The following statistical approaches were applied:
1. Conventional analyses.
2. Scaling of the bioequivalence interval based on the intra-subject variability of the reference product.

The evaluation analyses are described below:

1. **Conventional analyses:**

The conventional analyses were performed without and with using the pre-albuterol PD_{20} as covariate. These analyses were carried out for log-transformed (Ln) post-albuterol PD_{20} and Drug Activity Ratio (DAR). Analyses were carried out using SAS PROC MIXED.

a. Response Scale-Conventional Analyses without use of Pre-albuterol PD_{20} as Covariate

In these analyses, three models were considered: (1) a model that assumed no period effect, (2) a model that assumed that period effects might be present and (3) a model with period effects and the linear trend of the study day. The results of these analyses are summarized below in terms of point estimates and 90% confidence intervals for the ratio of test product average response over reference product average response.

Table 1. Response Scale-Conventional Analyses without use of Pre-albuterol PD_{20} as Covariate

	Ln(Post-Albuterol PD_{20})		Ln (DAR)	
Model	Point Estimate	90% CI	Point Estimate	90% CI
No Per. Eff.	80.24%	67.18, 95.83	89.35%	73.66, 108.37
With Per. Eff.	80.45%	67.40, 96.04	89.53%	73.53, 109.00
With Per. & Day	80.38%	67.36, 95.92	89.36%	73.32, 108.92

Comments:

i. Results of conventional analyses (no per., with per., and with per. & day) showed that the 90% confidence intervals for the log-transformed PD_{20} fall within the range of [ ]% previously considered by OGD for the approval of generic albuterol MDI's.

ii. Drug Activity Ratios (DAR) were calculated as secondary data analyses recommended in the OGD interim guidance. The DAR analysis is intended to assist an evaluation of adjustment of postdose PD_{20} for the baseline PD_{20} obtained on the same day. In addition, it serves as a

potential future reference in the development of a bioequivalence standard for albuterol inhalation aerosols.

iii. Note: The 1994 OGD interim guidance states that the primary data analysis of given bioequivalence data should be based on postdose PD_{20}.

b. Response Scale-Conventional Analyses with use of Pre-albuterol PD_{20} as Covariate

Several analyses were carried out in which Log pre-albuterol PD_{20} (LPRE) was used as a covariate. The summary of the analyses are the following:

i. All confidence intervals using LPRE as a covariate, regardless of the statistical model used, fell within the limits of [ ]%.

ii. The 90% confidence limits depended on which factors were included in the statistical model. One model had shown a lower limit of the 90% confidence interval ranged from [ ]%, and the upper limit of the 90% confidence interval ranged from [ ]%. For the overwhelming majority of the models considered, the lower 90% confidence limit was greater than 70%.

iii. These results (Analyses with use of Pre-albuterol PD_{20} as Covariate) appear to support the conclusion from the analyses without covariate, that the study data has established that the average response to the A. L. Labs product, divided by the average response to the reference product, Ventolin®, lies within the limits of [ ]%, for both LPOST and LDAR.

2. Scaling Of Bioequivalence Limits to the Reference Product Within-Subject Standard Deviation:

Two analyses were carried out for this scaling approach. The purpose of the two analyses was to assess whether bioequivalence had been demonstrated if the bioequivalence limits are scaled to the reference product within-subject standard deviation. These analyses used bootstrap methodology [specifically, the Bias-Corrected and Accelerated (BCa) method as described in the 1993 textbook of Efron and Tibshirani, 100,000 bootstrap samples per run] to obtain 90% confidence intervals for the quantity,

$$[Ln(muT) - Ln(muR)]/\sigma_{WR}$$

where: muT is the population geometric mean response for the Test product, muR is the population geometric mean response for the reference product, and σ_{WR} is the reference product within-subject standard deviation on the log scale. In the first analysis, it was assumed that there were no period effects in the study (Without Period Effect). In the second analysis, the analysis allowed for period effects (With Period Effect).

Table 2. The 90% bootstrap confidence limits

Model	Metric	90% bootstrap confidence Limits (Ln-Units)
Without Period Effect	Post-albuterol PD_{20}	-0.7221, -0.0889
	DAR	-0.5284, 0.1282
With Period Effect	Post-albuterol PD_{20}	-0.7916, -0.0744
	DAR	-0.5644, 0.1694

The bioequivalence limits to which these confidence intervals are compared are plus-or-minus $(\ln 1.25)/\sigma_{W0}$.
For the choices of σ_{W0}= 0.30, 0.25 and 0.20, these limits are as follows:

Table 3. Bioequivalence Limits

σ_{W0}	$(\ln 1.25)/\sigma_{W0}$	Bioequivalence Limits (Ln-units)
0.30	0.7438	-0.7438, 0.7438
0.25	0.8926	-0.8926, 0.8926
0.20	1.1157	-1.1157, 1.1157

Comments:

i. The scaling of bioequivalence limits become less stringent as the value of σ_{W0} is decreased, and more stringent as the value of σ_{W0} is increased.

ii. Using the analyses with no period in the model, the study would pass for LPOST for σ_{W0} =0.309 or lower, and would pass for LDAR for σ_{W0} =0.422 or lower.

iii. Using the analyses with period in the model, the study would pass for LPOST for σ_{W0} =0.282 or lower, and would pass for LDAR for σ_{W0} =0.395 or lower.

OVERALL COMMENTS:

1. The statistical analysis to determine bioequivalence of the test and reference products was based on the `response scale'. Analyses of the data were performed by the Division of Biometrics, HFD-700.

2. Results of conventional analyses with or without period effect showed that the 90% confidence intervals for the log-transformed PD_{20} fall within the range of (_% previously considered by OGD for the approval of generic albuterol MDI's.

   Note: The 1994 OGD interim guidance states that the primary data analysis of given bioequivalence data should be based on postdose PD_{20}.

3. Drug Activity Ratios (DAR) were calculated as secondary data analyses recommended in the OGD interim guidance. The 90% confidence intervals for the log-transformed DAR fall within the range of % . The DAR analysis is intended to assist an evaluation of adjustment of postdose PD_{20} for the baseline PD_{20} obtained on the same day. In addition, it serves as a potential future reference in the development of a bioequivalence standard for albuterol inhalation aerosols.

4. An alternative analysis, based on scaling the bioequivalence limits to the reference product's within-subject standard deviation, was conducted. The 90% confidence interval limits for the pivotal post-dose PD_{20} data pass the test for σ_{W0} = 0.282 or lower.

RECOMMENDATION:

1. The in vivo bioequivalence study conducted by A.L. Laboratories on its drug product, albuterol inhalation aerosol, 90 µg per actuation, lot #6403, comparing it to Ventolin® manufactured by Allen & Hanburys (a Division of Glaxo), has been found acceptable by the Division of Bioequivalence. Thus, A.L. Laboratories' albuterol inhalation aerosol, 90 µg per actuation is bioequivalent to the reference drug product, Ventolin® (Allen & Hanburys, a Division of Glaxo).

2. The firm has not yet conducted acceptable in vitro testing on the test product. Thus, the application is still incomplete.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ 2/27/97

Concur: /S/ Date: 4/29/97
Rabindra Patnaik, Ph.D.
fr ~~Acting~~ Director
Division of Bioequivalence

cc: ANDA 73-045 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File

Table 1
Comparative Formulations
(Weight of Ingredient per Canister)

Ingredients	Test*	Reference**	T/R
Albuterol, USP	mg	mg	0.840
Oleic Acid, NF	mg	mg	0.840
Trichloromonofluoromethane,NF (Propellant 11)	mg	mg	0.989
Dichlorodifluoromethane, NF (Propellant 12)	mg	mg	0.952
Total mg/Canister***	mg	mg	0.963

* 90 μg per dose delivered to patient, approximately 10% retained on mouthpiece.

* Includes a 15.9% overage to deliver a minimum of 200 doses per canister.

** The information of the RLD was provided in NDA #18-473, Volume #8.1, Annual Report R-08, Section C, covering the period of 01 June 1984 to 31 May 1985. The RLD includes a 10% formula overage.

*** Obtained by addition of the four ingredients.

Table 2
Comparative Formulations
(% Weight/Weight; %W/W)

Ingredients	Test Product % W/W	RLD % W/W
Albuterol, USP	%	%
Oleic Acid, NF	%	%
Trichloromonofluoromethane, NF (Propellant 11)	%	%
Dichlorodifluoromethane, NF (Propellant 12)	%	%
Total	%	%

Table 3
Comparative Formulations
(Weight of Ingredient per Actuation)
(Based on Drug Content)

Ingredients	Test*	Reference**	T/R
Albuterol, USP	μg	μg	1.00
Oleic Acid, NF	μg	μg	1.00
Trichloromonofluoromethane,NF (Propellant 11)	mg	mg	1.177
Dichlorodifluoromethane, NF (Propellant 12)	mg	mg	1.133
Total mg/Canister***	mg	mg	1.146

* Nominal 90 μg per actuation delivered to patient, approximately 10% of dose ex-actuator retained on mouthpiece.

* Includes a % %) overage to deliver a minimum of 200 actuations per canister. The overage accounts for filling variability and assures that the metering chamber of the aerosol valve is completely covered during the entire 200 labeled actuations. (Reference: 1 Aug 96 amendment)

* The information of the test product was provided in Volumes A1.1, p. 93; A8.1, p. 481; and A10.1 (Biobatch Identity section)

** The information of the RLD was provided in NDA #18-473, Volume 8.1, Annual Report R-08, Section C, covering the period of 1 Jun 84 to 31 May 85.

*** Obtained by addition of the four ingredients.

Table 4
Comparative Formulations
(Weight of Ingredient per Actuation)
(Based on Average Shot Weight)

Ingredients	Test	Reference**	T/R
Albuterol, USP	µg	µg	0.903
Oleic Acid, NF	µg	µg	0.903
Trichloromonofluoromethane,NF (Propellant 11)	mg	mg	1.06
Dichlorodifluoromethane, NF (Propellant 12)	mg	mg	1.02

Metering valves are designed to dispense volumetrically (A.J. Hickey, ed., *Pharmaceutical Inhalation Aerosol Technology*, Dekker, 1992, p. 173). The number of doses per canister is thus a function, in part, of the volume of the metering chamber, which affects the shot weight, and the weight of total suspension in the canister. Hence, formulation comparison based on average shot weights (Table 4) seems appropriate. This comparison indicates that:

> TEST PRODUCT IS WITHIN -10% AND +6% OF RLD ON VARIOUS INACTIVE INGREDIENTS,

which exceeds the 5% Q_2 limit recommended by the 17 Nov 94 OGD *Interim Inactive Ingredients Policy for* filing an ANDA. However, the Policy indicates that Q_2 may differ under certain circumstances, provided an *in vivo* study is conducted. It is noted that this ANDA was filed 23 Dec 88, preceding the Policy.

III. PARTICLE SIZE DISTRIBUTION BY CASCADE IMPACTOR

The Division of Bioequivalence guidance (June 27, 1989) recommends particle size determination by at least two different methods, including the pivotal cascade impactor data. The firm determined the particle size by using the following methods: cascade impactor, Malvern laser diffraction, and twin impinger.

Andersen Cascade Impactor:	1ACFM Non-viable Ambient Particle Sizing sampler (Mark II)
Number of stages:	8 stages
Atomizing chamber:	USP 23 metal throat
Flow rate:	30 L/min
Number of actuations per canister:	25

Note: USP 23 <601> specifies that the flow rate through the cascade impactor be within 2% of that specified by the manufacturer (28.3 L/min for the Andersen CI). Volume A7.1, p. 179 provides validation data for CI studies conducted at 25 L/min and 35 L/min. The firm concludes (1 Aug 96 amendment, Response 2) that differences in flow rate over this range had no significant effect on particle size results. In the reviewer's opinion, this conclusion is not justified in view of excessive variability. However, a 30 L/min flow rate can be accepted in view of the comparative nature of the CI data.

Note: The cascade impactor test product data reported in Volume A8.2, p. 565, contains an apparent typographical error for canister 2, stage 3, end sector (34747).

The cascade impactor apparatus (USP 23, Chapter 601) is used to determine the following:

(a) Total mass of drug released from the inhalation aerosol.
(b) Quantity of drug collected at each location of the cascade impactor device.
(c) Mass median aerodynamic diameter (MMAD; the diameter above and below which 50% of the mass of the drug reside).
(d) Geometric standard deviation (GSD).
(e) Respirable dose and respirable fraction.

Assay Method

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

MATERIAL BALANCE CALCULATION

The firm was requested to calculate material balance as defined in USP <601>, p. 1764. The firm's response (1 Aug 96 amendment, response 5, claims that the calculation is theoretical, based on the manufacturing formula. This is incorrect. USP specifically outlines this calculation, based on actual shot weight and measurement of drug concentration in the batch under consideration (assay of total drug in canister, and weight of total contents). Material balance enables a true estimate of drug recovered in the cascade impactor experiment relative to expected delivery. The firm's calculation, reported as "% mass balance" (1 Aug 96 amendment, Comment # 1 section, pp. 2-3), is NOT CORRECT. Actual expected drug delivery for test and RLD products was not determined. In addition, it is inappropriate for the firm to assume that the RLD has the same drug concentration in the suspension as does the test product (Reference: Table 1 of this review).

Table 6
Mass Median Aerodynamic Diameter (MMAD)
(microns)

	A.L. Laboratories (Lot 6403) MMAD, microns (GSD)				Ventolin (Lot Z31383LS) MMAD, microns (GSD)			
Spray #	Can 1	Can 2	Can 3	Mean	Can 1	Can 2	Can 3	Mean
6-30				2.62				2.32
91-115				2.55				2.32
176-200				1.98				2.37
Mean	2.48	2.67	2.60	2.58*	2.3	2.32	2.38	2.33 *

MMAD: mass median aerodynamic diameter in microns
GSD: geometric standard deviation
*: grand means are underlined
Each MMAD and associated GSD represents the data of one cascade impactor experiment.

Table 7
✓ Andersen Cascade Impactor: Respirable Dose and Respirable Fraction: Drug < 5.8 Microns

Shot #	"Respirable Dose" (μg/actuation)		
	Test (Lot 6403)	Reference (Lot Z31383LS)	T/R
6-30	35.8(17.2)	34.5(10.9)	1.04
91-115	44.8(15.6)	32.0(7.02)	1.40
176-200	48.2(17.8)	30.2(7.66)	1.60
OVERALL	42.9	32.2	1.33
Shot #	"Respirable Fraction"		
6-30	0.337(0.116)	0.373(0.124)	0.904
91-115	0.407(0.109)	0.332(0.070)	1.26
176-200	0.436(0.079)	0.326(0.085)	1.34
OVERALL	0.393	0.344	1.14

Data are given as mean (SD) of three experiments (i.e., three canisters).

Table 8
Andersen Cascade Impactor: Respirable Dose and Respirable Fraction: Drug < 4.7 Microns

Shot #	"Respirable Dose" (μg/actuation)		
	Test (Lot 6403)	Reference (Lot Z31383LS)	T/R
6-30	31.6(14.2)	33.0(10.1)	0.958
91-115	38.9(13.3)	30.7(6.21)	1.27
176-200	42.0(14.8)	28.7(6.54)	1.46
OVERALL	37.5	30.8	1.22
Shot #	"Respirable Fraction"		
6-30	0.299(0.094)	0.357(0.115)	0.838
91-115	0.353(0.093)	0.320(0.064)	1.10
176-200	0.382(0.062)	0.309(0.073)	1.24
OVERALL	0.345	0.329	1.05

Data are given as mean (SD) of three experiments (i.e., three canisters).

IV. PARTICLE SIZE DISTRIBUTION BY LASER DIFFRACTION

contract manufacturer of the test product, developed a nonstandard method for sizing particles from the aerosol cloud. The method involves The firm is inconsistent regarding the temperature - the 12 Jun 95 amendment (Vol. A8.2, p. 571, states that the canister is heated to the 1 Aug 96 amendment, p. 136, states that the canister is heated to The method uses a

The method is intended to provide a measure of drug particle size, rather than aerosol droplet size. The method is nonstandard, and is not a 'regulatory method' in the firm's ANDA.

Malvern Laser Diffraction

Sampling tube specifications are:

Diameter at base of tube:
Diameter at top of tube:

Length of tube:
Distance from the beam:
Distance above the beam:
Downpipe temperature:
MDI canister temperature:

Size determination was made on three canisters at beginning, middle and end sectors. Specific actuation (station) numbers were not provided. Volume distribution [D(v,0.5)] and a measure of dispersion, span {[D(v,0.9) - D(v,0.1)]/D(v,0.5)}, are listed in Table 9.

Table 9
Particle Size Delivered from
the Actuator (Mouthpiece) Laser[1,2]
(in microns)

Shot	Test Product (Batch #6403)				Reference Product (Batch #Z31383LS)			
	Can 1	Can 2	Can 3	Mean	Can 1	Can 2	Can 3	Mean
Beg				3.27 (4.0) [0.61]				2.92 (6.5) [1.04]
Mid				3.21 (3.5) [0.63]				2.97 (8.0) [0.94]
End				3.21 (3.4) [0.65]				2.90 (2.5) [0.92]
Mean	3.26	3.18	3.25	3.23	2.85	3.03	2.92	2.93

1 Span is given in brackets.
2 Particle size %CV is given in parentheses.

[3] Appears to be a mean result, not that of an individual experiment.

Comments:

1. The firm has reported 'best' runs, without stating the criteria for 'best.'
2. The firm should indicate whether the MDI canister is heated to
3. The median size volume distribution of the test product is about microns larger than for the RLD. However, the mean span of the test product, 0.63, is smaller than that of the RLD, 0.97.

V. SINGLE STAGE IMPACTOR USP APPARATUS 2 (TWIN IMPINGER): DEPOSITION OF EMITTED DOSE

The firm employed the Twin Impinger (single stage impactor apparatus 2, USP Chapter <601> Aerosols/Physical Tests) to determine the deposition of the emitted dose. Drug deposited on stage 2 is less than microns. Data are expressed as the amount of drug in stage 1 (upper chamber) and stage 2 (the lower chamber). The equations are presented on page 613, volume A8.2.

Table 10
Deposition of Emitted Dose*
(μg per actuation)

Deposition Stage	Test Product (Batch #6403)			Reference Product (Batch #Z31383LS)		
	Mean*	Range	%CV	Mean*	Range	%CV
Actuator	12.6		12.0	9.22		50.2
Upper Impinger (Stage 1)	40.9		5.75	33.2		9.79
Lower Impinger (Stage 2)	44.3		3.02	56.8		4.82
Unit Dose**	-	-	-	-	-	-
Respirable Percentage***	-	-	-	-	-	-

* Data are based on 5 canisters of test product and 5 canisters of RLD.

** USP <601> states that Unit Dose from mean data of Uniformity of Unit Spray Content study is to be used in calculation of Respirable Percentage.

*** USP <601> states that Respirable Percentage is to be calculated from the amount of drug in the lower impinger per discharge, as a percentage of the mean Unit Dose.

Comments:

1. The firm provides a mean Unit Dose of 90.44 µg for the test product and 97.29 µg for the RLD. The source for these numbers is not provided.

2. The firm reports Respirable Fraction data. However, in the absence of appropriate Unit Dose data, Respirable Fraction data cannot be calculated per USP recommendations.

3. Unit Dose data are requested for calculation of Respirable Fraction by the USP method. It is noted that comparative Unit Dose data for test and RLD products are provided in Volume B9.1, p. 21. However, the batch number of the RLD is not provided.

VI. SPRAY PATTERN AND PLUME GEOMETRY

A. Spray Pattern (12 Jun 95 submission)

The spray pattern and plume geometry are used to characterize the performance of the valve and actuator.

The spray pattern was determined on [redacted] spray per each of three canisters of test and RLD at each of three distances. Each can was placed in actuator and positioned, 2.5, 5.0 and 7.5 cm away and parallel to a 20 cm X 20 cm [redacted] spray. Single spray was fired (the canister was shaken before each spray) for each measurement. The resulting spots were viewed under UV light and the spray pattern was outlined with a pencil. Longest and shortest diameters of the spot were measured and the mean diameter was calculated.

Comment:

Freehand drawings of the spray patterns as submitted are imprecise and irregular, and cannot be interpreted. Data are unacceptable.

B. Spray Pattern (1 Aug 96 submission)

The firm was requested by letter of 18 Jul 96 to provide photographs of spray patterns. The firm conducted repeat spray patterns on the 'bio batches' of test and RLD products - these products were past their expiry dates at the time of retesting.

Comments:

1. Photographs of the data were submitted. Dimensions were based upon freehand drawings and do not appear from visual inspection to agree with the photographs. Accordingly, reported dimensions will not be tabulated.

2. Visual inspection of spray patterns reveals increasing diffuseness in the data for both test and RLD products as distance increases from cm.

3. Comparative data are acceptable.

C. Plume Geometry

Per the 1989 *In Vitro* Guidance, firms were encouraged to submit data on plume geometry, although these data are optional. Plume geometry data were not submitted.

VII. POTENCY

Potency is defined as the average amount of drug delivered per spray. The results are expressed as percent of labeled amount of drug delivered from the mouthpiece per spray.

Three random cans were tested. The cans were weighed and shots were sampled at the beginning (10-11), middle (100-101) and end (199-200) sprays. The loss in each canister weight was recorded.

Table 11
Potency as measured by Amount of Drug Delivered
(weight loss data are also listed)

	Test Product (Batch #6403)				Reference Product (Batch #Z31383LS)			
	Shots #	Mean	Range	% CV	Mean	Range	% CV	Mean T/R
Drug Delivered (μg/spray)	Sprays 11-12 (3 cans)	82.8		2.0	91.2		1.4	0.91
	Sprays 100-101 (3 cans)	94.0		4.0	102.0		4.8	0.92
	Sprays 199-200 (3 cans)	107.4		1.3	98.7		1.6	1.09
Weight Loss (mg/spray)	Sprays 11-12 (3 cans)	87.0		1.8	85.0		1.2	1.02
	Sprays 100-101 (3 cans)	86.8		2.0	84.9		2.2	1.02
	Sprays 199-200 (3 cans)	86.1		2.3	84.4		1.4	1.02

Comments:

1. The firm used three cans to determine the drug potency. The 1989 guidance requests potency determination for ten test and ten reference canisters.
2. The method used for determination of potency failed Methods Validation. No further review will be conducted until Division of Chemistry determines that the method is validated.

VIII. *IN VITRO* DEFICIENCIES

1. Pivotal *in vitro* comparative cascade impactor data are unacceptable. The assay appears to be inadequately sensitive to quantitate drug on each stage of the cascade impactor. The firm's use of per study, in spite of the recommendation in the 1989 Division of Bioequivalence Guidance to use 15 actuations, emphasizes the need for improved assay sensitivity.

2. Material balance (USP 23 <601>), as requested in the 18 Jul 96 letter to the firm, was not provided. This calculation requires a knowledge of the actual shot weight, and measurement of drug concentration in the test and reference canisters. Drug concentration in the canisters is determined by assay of total drug in canister, and weight of total contents. The firm's reported "% mass balance (1 Aug 96 amendment, Comment # 1 section, pp. 2-3) is not consistent with the USP material balance calculation.

3. Specific observations and concerns with the cascade impactor data will be discussed with the firm in the meeting scheduled for 9 Sep 96.

4. Particle size distribution by laser diffraction reports "best 3 results" without providing criteria for selection of best runs. The result reported for canister # 3 (test product), middle canister sector, appears to be a mean result, not that of an individual experiment. No indication of specific station (actuation) numbers were provided to identify beginning, middle and end canister sectors.

5. USP 34 <601> requests for single stage impactor apparatus 2 that unit dose from mean data of the Uniformity of Unit Spray Content study be used in the calculation of Respirable Percentage. The firm states that the mean unit dose for test and RLD products is 90.44 µg for the test product and 97.29 µg for the RLD. It is noted that the firm did not conduct Uniformity of Unit Spray Content (USP <905>) on both test and RLD products, thus Respirable Percentage data cannot be determined based on the USP method. The source of the mean unit dose data is not apparent.

6. Potency/unit spray content data will not be reviewed until Division of Chemistry determines that the method is validated.

7. Specifications or revisions to specifications need to be considered for various tests, including respirable dose.

8. Particle size (distinct from particle size distribution) from the aerosol by

microscopy, a standard test recommended by USP <601> to reveal large solid particles and agglomerates, has not been provided.

IX. RECOMMENDATION

The firm should be informed of the *in vitro* deficiencies cited above.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

/S/

Wallace P. Adams, Ph.D.
Office of Generic Drugs

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ 9/3/96

/S/

Concur: _____ Date: 9/3/96
for Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 73-045 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Wahba), Drug File, Division File

SEP - 3 1996

Albuterol Inhalation Aerosol (MDI)
90 µg/actuation
ANDA **73-045**
Reviewer: Z.Z. Wahba
73045s2.695

A.L. Laboratories
Baltimore, MD
Submission Dates:
June 12,1995
June 22,1995

Further Review for the In-Vivo Bioequivalence Study (Continuation of the Review Dated July 17, 1996)

I. BACKGROUND:

The firm submitted an application containing data from a pharmacodynamic bioequivalence study based on bronchoprovocation model employing a methacholine (MC) challenge methodology, and a safety evaluation study on its albuterol metered dose inhaler (MDI), 90 µg/actuation. The application also contains *in-vitro* performance data comparing the test product and the reference product, Ventolin® manufactured by Allen & Hanburys (a Division of Glaxo).

II. INTRODUCTION:

Albuterol is a synthetic sympathomimetic amine. It is a selective $beta_2$-adrenergic bronchodilator. It is administered either by inhalation or orally for the symptomatic relief of bronchospasm. When the drug is administered by inhalation, it produces significant bronchodilation in patients with reversible obstructive airway disease within 15 minutes and its effects are demonstrable for 3 to 4 hours. Its mechanism of action is due to its bronchodilation effect that results from relaxation of the smooth muscles of the bronchial tree. In patients with reversible airway obstruction, albuterol decreases resistance of the airways.

Each actuation delivers from the mouthpiece 90 µg of albuterol. Administration of albuterol MDI at recommended doses (one or two actuations) produces very low drug concentrations in accessible biological fluids such as blood or urine. Furthermore, following its topical application, the relevance of systemic levels of albuterol to its action in the lung is obscure. Therefore, on January 27, 1994, the Office of Generic Drugs issued a guidance to document the *in vivo* bioequivalence of multi-source albuterol MDI's based on pharmacodynamic methodology.

The 1994 OGD interim guidance recommended performance of two *in vivo* studies: (1) a pharmacodynamic bioequivalence study using a challenge (bronchoprovocation) design and (2) a safety evaluation study. This latter study is more appropriately termed a comparative systemic pharmacodynamic evaluation.

The two studies presented in this application are based on the 1994 OGD interim guidance.

III. OBJECTIVE:

The objective of the bronchoprovocation bioequivalence study is to demonstrate in vivo bioequivalence between the test product, A.L. Laboratories' Albuterol Metered Dose Inhaler (MDI) and the reference listed drug, Ventolin® Inhalation Aerosol.

IV. BRONCHOPROVOCATION BIOEQUIVALENCE STUDY:

A. Summary of Study Design:

Clinical study project #135-01-10647. The study protocol was reviewed and approved by the Institutional Review Board of the testing organization on May 02, 1994.

B. Protocol Title:

A bronchoprovocation study comparing two formulations of Albuterol Metered-Dose Aerosol Inhaler in patients with mild to moderate asthma.

C. Sponsor:

A.L. Laboratories, Inc.
The Johns Hopkins Bayview
Research Campus
333 Cassell Drive, Suite 3500
Baltimore, Maryland 21224

D. Clinical Facility:

Principle Investigator:
Project Director:

E. Study Period:

May 1994 to May 1995

F. Subject Selection:

The subject selection criteria for this study were carried out according to the OGD guidance.

Patients were trained in the correct use of the MDI prior to

each day's testing with the InspirEase® training device to assure a consistent inspiratory flow rate and duration. For actual dosing, patients were required to place the inhaler in their mouths with their lips forming a seal around the mouthpiece. Patients were required to actuate the MDI and at the same time, start a slow sustained inhalation over a 6-9 second period. After inhalation, patients were required to hold their breath for 8-10 seconds before a controlled exhalation. The investigator and patients remained blinded as to which treatment was administered during each period.

BASELINE QUALIFICATION

Patients were required to perform repeated baseline FEV_1s at the start of each day. In most cases, three baseline FEV_1s were within 5% of each other.

Each study day consisted of a pre-albuterol methacholine challenge followed at least 3 hours later by administration of the assigned albuterol treatment and a post-albuterol methacholine challenge. Per protocol, each dosing period was separated by at least 24 hours. The reviewer notes, however, that the stated protocol would allow study day intervals of not less than 23 hours.

Before proceeding with the albuterol treatment on each day, subjects were required to meet the following baseline criteria:

1. An FEV_1[1] [ ]% of predicted value for age, height and gender.
2. An FEV_1 within [ ]% of the qualifying day FEV_1
3. FEV_1, due to the saline control not less than a [ ]% decrease from baseline FEV_1.
4. A pre-albuterol PD_{20}[2] within a four-fold dilution [ ]%) of the qualifying day PD_{20} (see Deviation from Subject Inclusion Criteria section J of this review).

FEV_1: Forced Expiratory Volume of the lung in one second.

PD_{20}: The cumulative dose of the challenge agent (methacholine) required to drop the FEV_1 value by [ ]% below the saline control FEV_1.

G. Study design:

Randomized, two-treatment, four-period, two-sequence, crossover double blind study on four separate days, employing 25 mild to moderate asthma patients. A single dose (90 µg/actuation) was administered during each treatment period.

Treatment Sequences:

Period	Visit 1	Visit 2	Visit 3	Visit 4
Sequence 1	T	R	R	T
Sequence 2	R	T	T	R

T=test product R=reference product

Dosing was performed for each patient at approximately the same time (within one hour) for each treatment period. On methacholine challenge days, dosing with albuterol MDI occurred 15 minutes prior to initiation of the methacholine challenge test.

Randomization:
a. Sequence #1: Subjects #102, 104, 105, 109, 114, 116, 118, 119, 121, 124, 126 and 127.

B. Sequence #2: Subjects #101, 103, 106, 108, 110, 113, 115, 117, 122, 123, 125, 128 and 129.

Canister Camouflage:
Canisters and actuators were camouflaged with silver colored, plastic coated cloth tape in such manner as not to interfere with product performance. It is also noted that test product and reference product actuators were both blue in color.

H. Treatment Plan: (vol. A8.1, page #030)

1. Bioeqivalence Study Products:

a. Test Product:

Albuterol Metered Dose Inhalation Aerosol.
90 µg/actuation
Manufacturer: CCL Laboratories Ltd., England
Lot #6403; Lot Size-total units filled units (Lot Size, minus rejects units); manufacture date: July 1993; Valve: mm Silver µL); Manufacturer:
Actuator: Cadet Blue, L-Shape Actuator, #3013, Manufacturer:

Dose: one inhalation of A.L. Lab's albuterol MDI (90µg/actuation);

b. Reference Product:

Ventolin® (Albuterol Metered Dose Inhaler)
90 µg/actuation
Manufacturer: Allen & Hanburys, Division of Glaxo
Lot #Z31383LS
Expiration Date: March 1996

Dose: one inhalation of Ventolin® inhalation aerosol (90µg/actuation), Allen & Hanburys.

2. Other Drug Products:

a. Screening for the Dose Response:

Ventolin® Aerosol Inhaler
90 µg/actuation
Manufacturer: Allen & Hanburys, a Division of Glaxo
Lot #Z31443MS, Expiration Date: March 1996
Lot #Z31473MS, Expiration Date: March 1996
Lot #4ZPA183, Expiration Date: December 1996

b. Challenge Testing:

Product: Methacholine chloride (Provocholine®)
100 mg/5 mL vial for reconstitution
Manufacturer: Roche Laboratories
Lot #0033, Expiration Date: April 1, 1995
Lot #0038, Expiration Date: November 1, 1995

I. **Subjects:**

Demographic Information

The total number of patients screened for the study	**87** patients were screened but the firm's demographic table provided information for 84 patients only. Males= 34 Females= 50
Number of patients who failed screening and were discontinued	**58** subjects failed screening: Details a. **24** subjects had baseline FEV_1s less than 80% of predicted value b. **10** subjects failed to demonstrate a suitable airway response to doses of methacholine below 4 mg/ml c. **19** subjects failed to meet the necessary airway responsiveness to one or two actuations of albuterol d. **5** Subjects were ineligible because of medical issues (4 were over-weight and 1 was taking concomitant medication).
Number of Patients who passed the inclusion/ exclusion and screening criteria for entry the biostudy	**29** patients Males= **15** Females= **14**
Number of patients who completed the biostudy	**25** patients (#101-106, 108-110, 113-119, and 121-129)completed the biostudy. Males= **12** Females= **13** Out of 29 patients only 4 patients (#107,111, 112 and 120) did not complete the study for various reasons (for details see Vol. #8.1, p #076)

J. Deviation from Subject Inclusion Criteria:

1. Subject #103 did not meet the criteria of (PD_{20} after 2 actuations)/(baseline PD_{20}) $\geq$ 8.0 and (PD20 after 2 actuations)/(PD_{20} after 1 actuation) $\geq$ 2.0, the ratios were 7.4 and 1.8, respectively.

2. Subject #108 did not meet the criteria of (PD_{20} after 2 actuations)/(baseline PD_{20}) $\geq$ 8.0 and (PD20 after 2 actuations)/(PD_{20} after 1 actuation) $\geq$ 2.0, the ratios were 6.4 and 1.9, respectively.

3. Subject #119 did not meet the criteria of (PD_{20} after 2 actuations)/(baseline PD_{20}) $\geq$ 8.0, the ratio was 7.7.

4. There was a number of baseline PD_{20} on some study days that showed values outside the range of % of the qualifying day PD_{20} as recommended by the Interim Guidance. An amendment to the protocol was approved by the Institutional Review Board (IRB) for Human Subjects Research, Johns Hopkins Health System on October 25, 1994 to broaden baseline PD_{20} criteria to be within a fourfold dilution %) of the value measured on the qualifying day. (See Vol. A8.1, Clinical Summary Section, page #072 and Clinical Appendix I, pages #147-149).

K. Visits Plan:

The twenty-five subjects who completed the biostudy did so in a minimum of 4 and a maximum of 7 visits. Eight, nine, five and three subjects completed the study in 4, 5, 6 and 7 visits, respectively.

L. Study Validation:

Validation of Methacholine (MC) challenge methodology was performed based on intra-day and inter-day reproductivity of MC PD_{20} values. FEV_1 measurements were used to evaluate the study validation.

Four subjects (#101, 102, 103 and 104) were used to evaluate the validation of the methacholine challenge method. Intra-day precision was evaluated by comparing two methacholine challenge tests conducted at an interval of at least three hours. Inter-day precision was measured by comparing the methacholine challenges tests conducted on five different days (Vol. A8.1, pp 114-146)). The arithmetic average of the PD_{20}s for intra-day CV was 64% and for inter-day was 68% (vol. A8.1, p 114).

ACCURACY OF DATA

PD_{20} values:

The pharmacodynamic data are given in this application in the form of MC PD_{20} values. The reviewer performed spot-check calculations to determine the accuracy of the PD_{20} values.

The sponsor calculated the PD_{20} values by linear interpolation between the last two FEV_1 values and the respective cumulative doses of methacholine.

To verify these data, the reviewer calculated the PD_{20} values using the following formula based on modification of a formula in HISTAMINE AND METHACHOLINE TESTS:✓Tidal Breathing Method, Laboratory Procedure and Standardisation, By E.F. Juniper, D.W. Cockcroft and F.E. Hargreave, 1991, p 28-29.

$$PD_{20} = D1 + \frac{(D2 - D1)(20 - R1)}{(R2 - R1)}$$

Where:

D1= second to last cumulative methacholine dose (<20% FEV_1 fall)
D2= last cumulative methacholine dose (>20% FEV_1 fall)
R1= % fall in FEV_1 after D1 relative to saline control.
R2= % fall in FEV_1 after D2 relative to saline control.

The results of calculations on random spot-check of validation study (pages 125-134, Vol. A8.1).

APPEARS THIS WAY
ON ORIGINAL